

Prevalence of Serious Bleeding Events and Intracranial Hemorrhage in Patients Receiving Activated Protein C: A Systematic Review and Meta-analysis

Ajmal Khan MD DM, Ritesh Agarwal MD DM, Ashutosh N Aggarwal MD DM, and Dheeraj Gupta MD DM

BACKGROUND: Activated protein C reduces 28-day mortality in patients with severe sepsis, but its anticoagulant properties entail a risk of bleeding. **OBJECTIVE:** The aim of this systematic review was to evaluate the prevalence of serious bleeding events in patients receiving activated protein C. **METHODS:** We searched the MEDLINE and EMBASE databases for studies that described the prevalence of serious bleeding events and intracranial hemorrhage in patients receiving activated protein C. We calculated the bleeding rates by calculating proportions and 95% CIs for each study, and then pooled the data to derive a pooled proportion and 95% CI. **RESULTS:** Our search yielded 17 studies, which included 10,679 patients. The occurrence of serious bleeding events in patients receiving activated protein C ranged from 0.5% to 9.6%, and the pooled prevalence was 3.3% (95% CI 2.4–4.4%) by the random effects model. The occurrence of intracranial hemorrhage ranged from 0% to 1.4%, and the pooled prevalence was 0.44% (95% CI 0.31–0.6%). Sensitivity analysis showed a higher prevalence of bleeding in the observational studies than in the randomized controlled trials. There was substantial clinical and statistical heterogeneity, but no evidence of publication bias. **CONCLUSIONS:** Activated protein C is associated with significant risk of bleeding, so strict inclusion and exclusion criteria should be set prior to administering activated protein C. *Key words:* *drotrecogin alfa; activated protein C; serious bleeding event; intracranial hemorrhage; sepsis.* [Respir Care 2010;55(7):901–910. © 2010 Daedalus Enterprises]

Introduction

Severe sepsis, defined as sepsis with organ dysfunction, hypoperfusion, or hypotension, remains a major cause of morbidity and mortality in adults.^{1,2} Important concepts in the management of severe sepsis have emerged in recent years, and the approval of activated protein C for sepsis management has been an active topic of discussion. In the landmark Recombinant Human Activated Protein C World-

wide Evaluation in Severe Sepsis (PROWESS) study, activated protein C was efficacious in reducing sepsis-related mortality.³ That study triggered considerable debate because both the United States Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products approved activated protein C for specific patient subgroups (ie, those with Acute Physiology and Chronic Health Evaluation II scores > 25 in the United States, and \geq 2-organ failure in Europe) on the basis of that trial. However, later studies failed to recapitulate similar benefit in patients with low risk of death.⁴

Because of its antithrombotic and profibrinolytic properties, bleeding complications are the most important serious adverse events associated with activated protein C. Thus, it is prudent to anticipate increased risk of bleeding with activated protein C, which dictates extreme caution with patients at increased risk of bleeding due to severe sepsis or its complications. To derive any benefit from activated protein C, the potential risk for bleeding needs to

Ajmal Khan MD DM, Ritesh Agarwal MD DM, Ashutosh N Aggarwal MD DM, and Dheeraj Gupta MD DM are affiliated with the Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

The authors have disclosed no conflicts of interest.

Correspondence: Ritesh Agarwal MD DM, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. E-mail: riteshpgi@gmail.com.

be weighed carefully prior to its administration. Numerous analyses have been performed to assess the safety of activated protein C.^{5,6-11} The occurrence of bleeding that is directly attributable to activated protein C ranges from 2.8% to 5.3%.⁵ The prevalence of intracranial hemorrhage ranges from 0.6% to 1.4%, which is only marginally higher than the 0.4% rate of spontaneous intracranial hemorrhage in the critically ill.⁷ However, all those analyses included data only from controlled clinical trials. Usually the strict conditions employed in randomized controlled trials (RCTs) cannot be practiced in normal clinical situations because of logistical difficulties and lack of institutional guidelines for intensive-care practitioners, and might cause difficulties in extrapolating data from controlled trials to daily practice. Also, none of the reviews has used a systematic search method for identifying studies that utilized activated protein C.

The aim of this systematic review and meta-analysis was to analyze the rate of serious bleeding events in patients who received activated protein C for severe sepsis by including data from both RCTs and observational studies.

Methods

Search Strategy

We first searched the literature for systematic reviews of the prevalence of bleeding in patients who received activated protein C. No systematic reviews were found. Our search strategy then aimed to identify studies that described the prevalence of serious bleeding events and intracranial hemorrhage. No specific inclusion criteria were defined for inclusion in this review; however, we recorded the criteria used by other authors. We reviewed all published articles that reported the prevalence of bleeding rates in patients who received activated protein C, and we restricted the review to papers in English. Each of us independently searched the MEDLINE and EMBASE databases for relevant studies published from 1989 to 2009, using the following free text terms: "activated protein C," "activated protein C AND multi-organ dysfunction," "activated protein C AND septic shock," "activated protein C AND severe sepsis," "activated protein C AND pancreatitis," "drotrecogin alpha," "drotrecogin alpha activated," "drotrecogin alpha AND bleeding," and "human recombinant activated protein C."

The search was supplemented with several additional search strategies to identify relevant articles not found in the databases. We hand-searched the indices of *Critical Care Medicine* (2001–2009) and *Intensive Care Medicine* (2001–2009). We reviewed the reference lists of primary studies, reviews, and editorials. In addition, we reviewed our personal files. We excluded abstracts, editorials, case reports, studies that described bleeding rates in < 20 patients, and studies in which the total number of patients with severe sepsis (ie, denominator) was not reported.

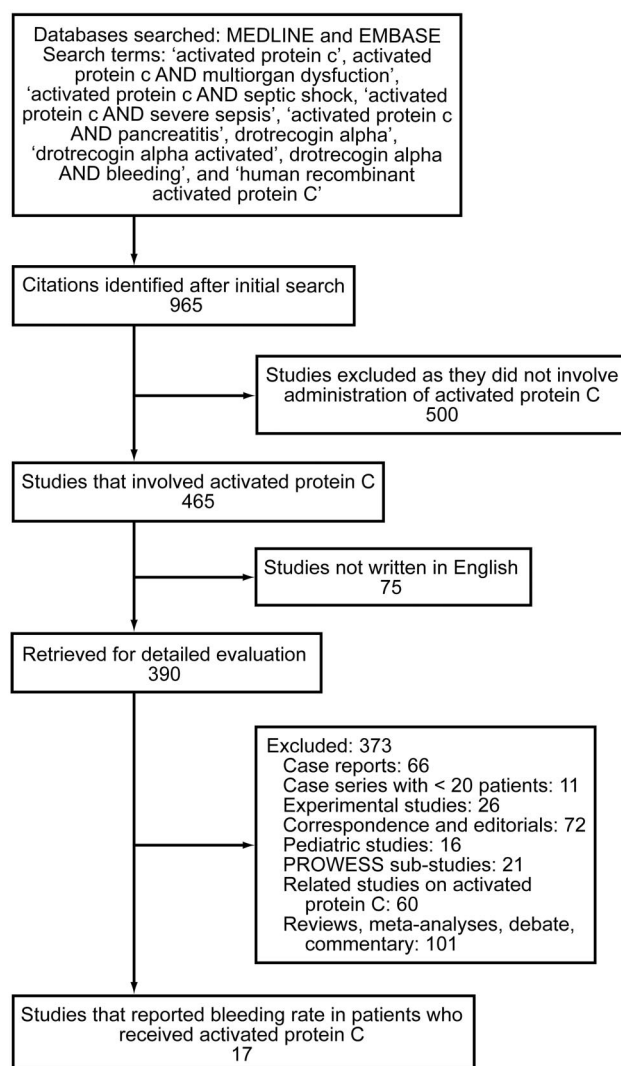


Fig. 1. Study-selection process for this systematic review. PROWESS = Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis trial³.

Initial Review of Studies

The initial database created from the electronic searches was compiled and all duplicate citations were eliminated. The first and second authors screened these citations, without blinding, by title and abstract review, to capture the relevant studies. Any disagreement was resolved by discussion between the authors. This database was then screened again to include only primary articles, and the full text of each citation was obtained and reviewed. Studies were eligible for inclusion if they reported the bleeding rates in patients who received activated protein C.

Data Abstraction

Data were recorded on a standard data-extraction form. We extracted:

Table 1. Baseline Characteristics of the Study Populations in the Studies Included in This Systematic Review

First Author	Year	Patients (<i>N</i>)	Age (mean ± SD)	APACHE II Score (mean ± SD)	Organ Dysfunction Score						Surgical	Medical
					0	1	2	3	4	5		
Randomized Controlled Trials												
Bernard ²¹	2001	90	58 ± 14	16.8 ± 5.3	0	61	32	7	0	0	29	71
Bernard ³	2001	850	60.4 ± 17.2	16.8 ± 7.6	1	215	270	215	119	37	225	625
Abraham ⁴	2005	1,333	58.8 ± 16.8	18.2 ± 5.8	9	864	356	104	ND	ND	504	829
Levi ²⁸	2007	1,935	59 ± 16	23.9 ± 7.5	152	547	643	402	194	ND	661	1,274
Dhainaut ³⁴	2009	193	62 ± 13.4	28.1 ± 8.1	2.8 ± 1*	ND	ND	ND	ND	ND	ND	ND
Prospective Observational Studies												
Bernard ²²	2004	273	59.1 ± 17.4	23.4 ± 7.4	ND	ND	199	74	ND	ND	69	204
Vincent ²³	2005	2,378	59.1 ± 16.9	22 ± 7.4	0	370	2,008	ND	ND	ND	973	1,405
Decruyenaere ³³	2009	97	61.4 ± 18.5	25.3 ± 8.6	ND	ND	20	31	29	17	ND	ND
Retrospective Observational Studies												
Kubler ²⁴	2006	302	44.7 ± 18.2	25.3 ± 9.5	ND	0	20	46	236	ND	158	144
Spriet ²⁵	2006	23	59 ± 58	25 ± 26	3.5 ± 3*	ND	ND	ND	ND	ND	ND	ND
Kanji ²⁷	2007	261	56 ± 17	31 (26–36)†	ND	1	51	89	90	29	31	230
Bertolini ²⁶	2007	668	57.9 ± 16.8	ND	ND	ND	ND	ND	ND	ND	311	357
Ridley ²⁹	2008	351	61.8 ± 16.3	23.2 ± 7.2	ND	ND	ND	ND	ND	ND	177	174
Rowan ³⁰	2008	1,292	58.8 ± 16	21.9 ± 6.9	ND	60	238	498	398	98	353	939
Taylor ³¹	2008	100	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Wheeler ³²	2008	274	57 ± 18	ND	ND	ND	ND	ND	ND	ND	90	184
Gentry ³⁵	2009	73	58.3 ± 14.7	24.7 ± 7.1	ND	ND	ND	ND	ND	ND	ND	ND

APACHE = Acute Physiology and Chronic Health Evaluation

IQR = interquartile range

ND = no data available

 * Data are mean \pm SD.

† Data are median (IQR).

- Publication details: title, authors, location of study, and other citation details
- Type of study: prospective or retrospective; observational or RCT
- Age, illness-severity score, number of organ dysfunction, baseline prothrombin time (and/or international normalized ratio), activated partial thromboplastin time, and number of surgical versus medical patients
- Definitions of serious bleeding event and intracranial hemorrhage
- Prevalence of serious bleeding events and intracranial hemorrhage during infusion of activated protein C and at 28 days after activated protein C, where the numerator was either serious bleeding event or intracranial hemorrhage, and the denominator was number of patients who had received activated protein C

Determination of the Pooled Effect

We used commercial statistics software (StatsDirect 2.7.7, StatsDirect, Cheshire, United Kingdom) to perform the statistical analysis. We calculated the bleeding

rates as proportions and 95% CIs for each study, and then pooled the data to derive a pooled proportion and 95% CI. For the purpose of proportion meta-analysis, the proportions were first turned into a quantity (the Freeman-Tukey variant of the arcsine square-root transformed proportion) suitable for the usual fixed and random effects summaries.^{12,13} The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using DerSimonian weights for the random effects model¹⁴ in the presence of significant heterogeneity.

Assessment of Heterogeneity

The impact of heterogeneity on the pooled estimates of the individual outcomes of the meta-analysis was assessed with the Cochran Q statistic and I^2 test, which measures the extent of inconsistency among the results of the studies, which were interpreted as the approximate proportion of total variation in study estimates that was due to heterogeneity rather than sampling error.¹⁵ An I^2 value more than 40–50% indicates significant heterogeneity. As the Cochran Q test has a low sensitivity for detecting heterogeneity, a P value of $< .1$ was considered significant for the presence of statistical heterogeneity.¹⁶

SERIOUS BLEEDING AND INTRACRANIAL HEMORRHAGE DURING ACTIVATED PROTEIN C

Table 2. Inclusion and Exclusion Criteria and Definitions of Serious Bleeding Event

First Author	Year	Study Type	Inclusion Criteria	Exclusion Criteria	Definition of Serious Bleeding Event
Bernard ²¹	2001	Double-blind multicenter prospective RCT	As per PROWESS trial*	As per PROWESS trial	As per PROWESS trial, except no investigator classified serious bleeding event was needed
Bernard ³	2001	Double-blind multicenter prospective RCT	PROWESS trial	PROWESS trial	PROWESS trial
Bernard ²²	2004	Open-label multicenter prospective	As per PROWESS trial	As per PROWESS trial	As per PROWESS trial, except no investigator classified serious bleeding
Vincent ²³	2005	Open-label multicenter prospective	As per PROWESS trial	As per PROWESS trial	As per PROWESS trial
Abraham ⁴	2005	Double-blind multicenter prospective RCT	Severe sepsis with organ dysfunction	High risk of death, defined by APACHE score > 25, multi-organ failure. Rest same as PROWESS trial.	As per PROWESS trial
Kubler ²⁴	2006	Open-label multicenter retrospective	As per PROWESS trial	As per PROWESS trial	Not defined
Levi ²⁸	2007	Double-blind multicenter prospective RCT		Contraindication to low-molecular-weight heparin or unfractionated heparin; required a higher dose of heparin or needed other anticoagulant; acute or chronic renal failure. Rest as per PROWESS trial.	Fatal bleeding, intracranial hemorrhage, bleeding at location such as retina, major hemarthrosis, spinal hemorrhage, or other life-threatening bleeding
Spriet ²⁵	2006	Open-label retrospective	As per PROWESS trial	As per PROWESS trial	Intracranial hemorrhage, life-threatening bleeding, or a requirement of ≥ 3 units of blood per day for 2 consecutive days
Kanji ²⁷	2007	Open-label retrospective	As per PROWESS trial and Canadian monograph	As per PROWESS trial and Canadian monograph	Intracranial hemorrhage, any bleed classified as serious by physician, requiring 3 units of packed red blood cells for 2 consecutive days
Bertolini ²⁶	2007	Open-label retrospective	As per PROWESS trial and off-label use	As per PROWESS trial	As per PROWESS trial, except blood transfusion of > 2 units of packed red blood cells
Ridley ²⁹	2008	Open-label retrospective	Severe sepsis and ≥ 2 organ dysfunction	Not defined	Not defined
Rowan ³⁰	2008	Open-label multicenter	As per PROWESS trial	Not defined	Not defined
Taylor ³¹	2008	Open-label single-center retrospective	As per PROWESS trial	As per PROWESS trial	As per PROWESS trial, and a bleeding event that met the criteria for serious adverse event
Wheeler ³²	2008	Observational multicenter retrospective	Documented severe sepsis with 1 organ dysfunction and received activated protein C as physician-directed treatment	As per PROWESS trial except activated protein C as part of other study or for reasons other than severe sepsis; taking part in other study and fewer limitations for timing of administration; comorbid illness and risk associated with bleeding; weight > 135 kg; renal failure	As per PROWESS trial
Decruyenaere ³³	2009	Phase IV open-label multicenter prospective	As per PROWESS trial	As per PROWESS trial	Not defined
Dhainaut ³⁴	2009	Multicenter double-blind prospective RCT	As per PROWESS trial	As per PROWESS trial, and expected to require major surgery in next 3 d, received drug within 30 d that had not received regulatory approval	Not defined
Gentry ³⁵	2009	Phase IV open-label retrospective	As per PROWESS trial	As per PROWESS trial	An acute (< 48 h) hemoglobin decline of at least 2 g/dL (except central-nervous-system bleed), transfusion requirement of ≥ 4 units over 48 h, objective evidence of bleed, documented by physician

* See Table 4 for the PROWESS trial³ inclusion and exclusion criteria.
RCT = randomized controlled trial

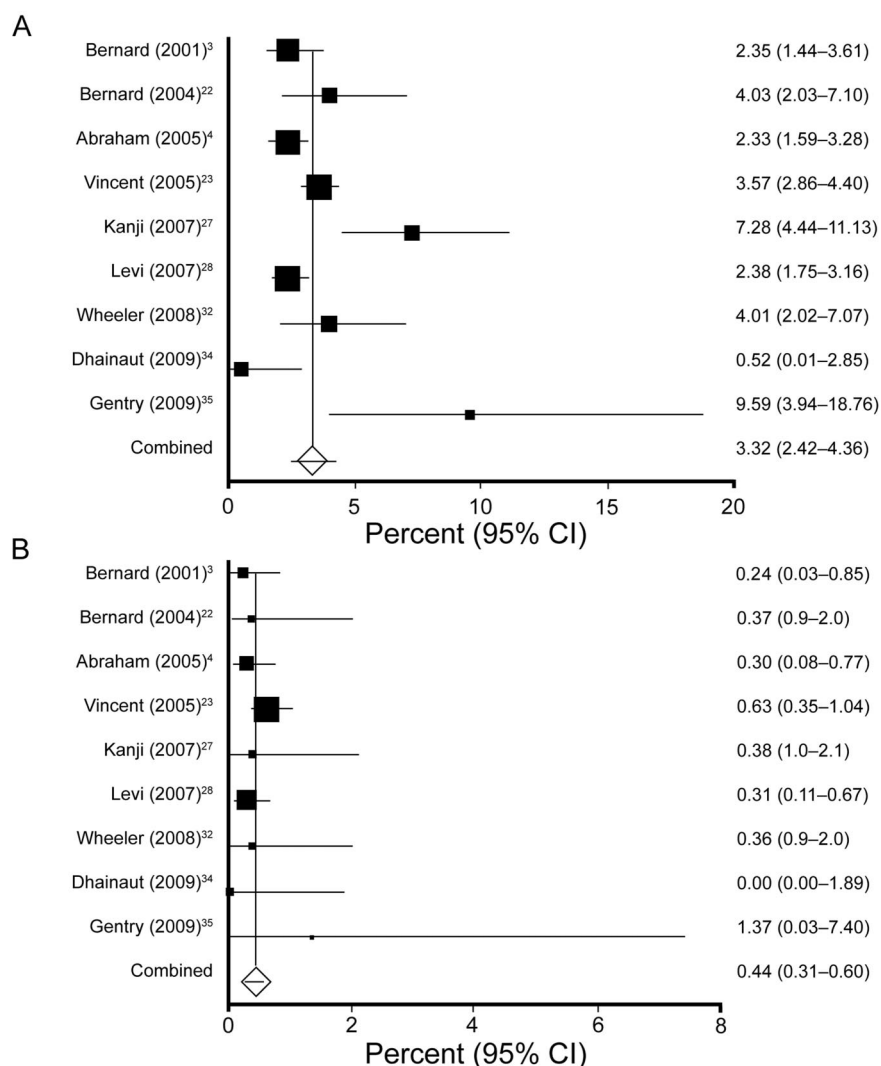


Fig. 2. Prevalence of serious bleeding events (A) and intracranial hemorrhage (B) during infusion of activated protein C (random effects model). The prevalence of serious bleeding events and intracranial hemorrhage in the individual studies is represented by a square (percentage), through which runs a horizontal line (95% CI). The diamonds represent the pooled prevalence from the studies.

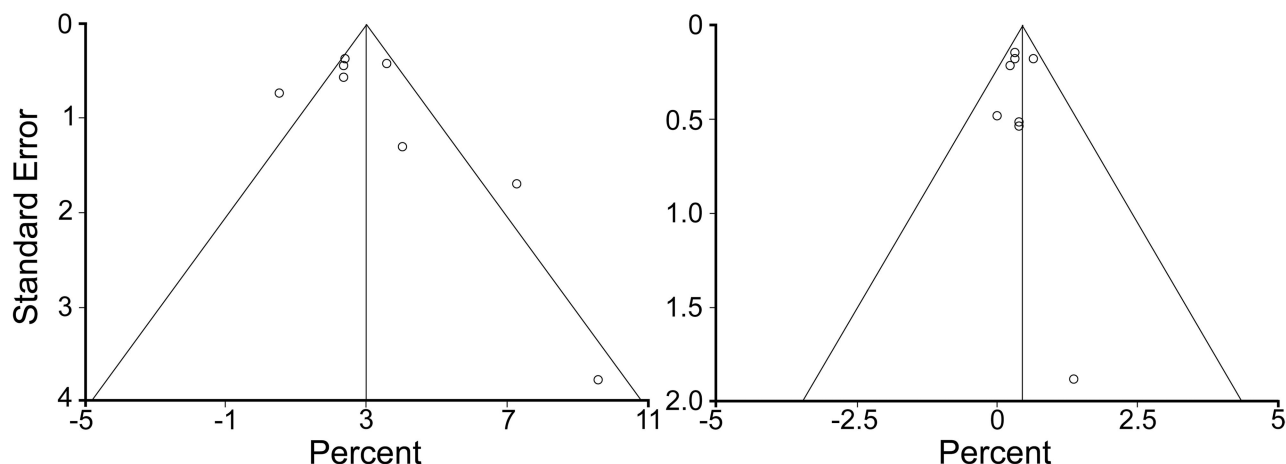


Fig. 3. Funnel plots comparing the proportions versus the standard error of the proportions for intracranial hemorrhage (left) and serious bleeding events (right) during infusion of activated protein C. The circles represent the trials included in the meta-analysis. The line in the center indicates the summary proportion. The other lines represent the 95% CIs. There was no evidence of publication bias.

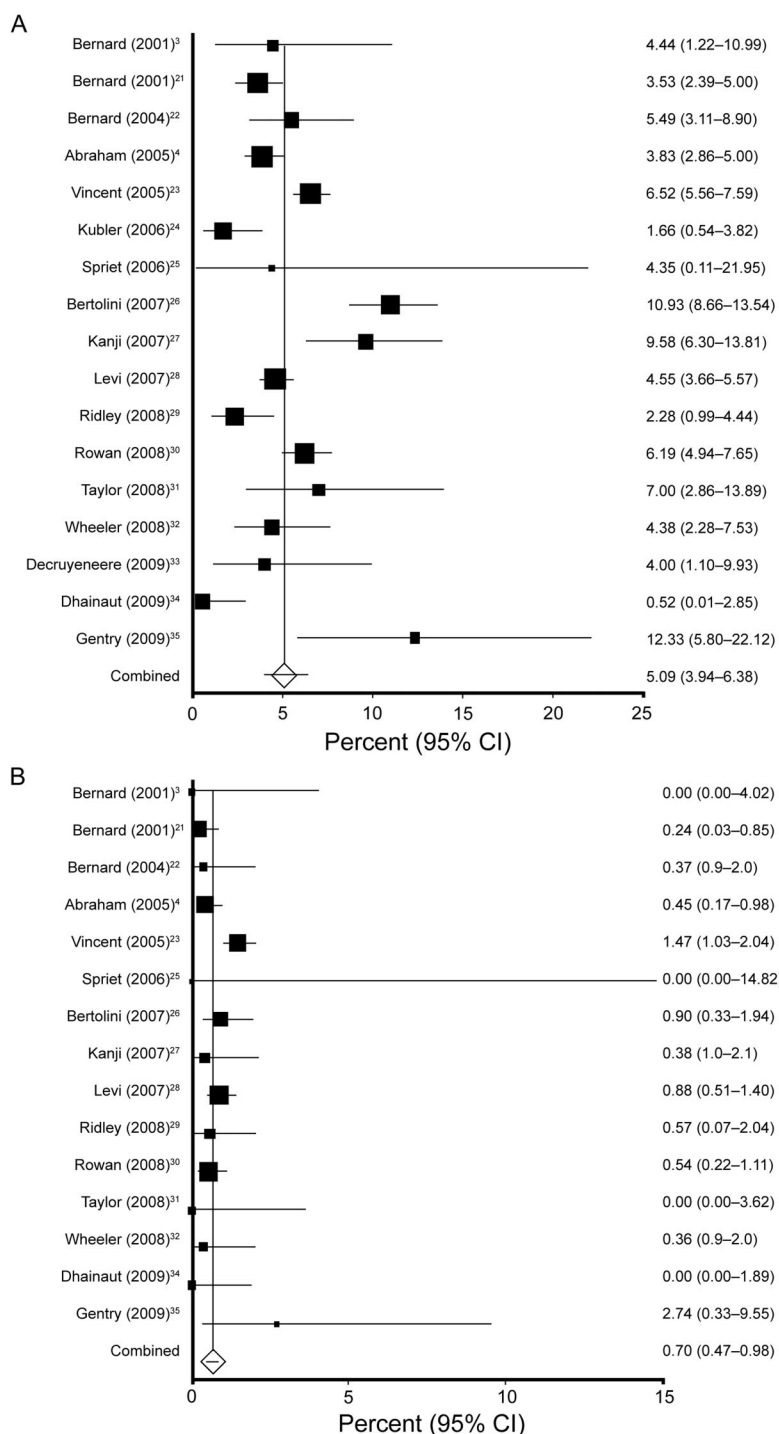


Fig. 4. Prevalence of serious bleeding events (A) and intracranial hemorrhage (B) at 28 days in patients who had received activated protein C (random effects model).

Assessment of Publication Bias

We checked for the presence of publication bias with the Begg's funnel plot.¹⁷ The funnel plot is a measure of proportion (on the X axis) against the standard error of

proportion (on the Y axis). In the graph, each circle represents a study in the meta-analysis. The line in the center indicates the summary proportion, and the other 2 lines indicate the 95% CI. In the absence of publication bias, the proportion estimates from smaller studies are expected to

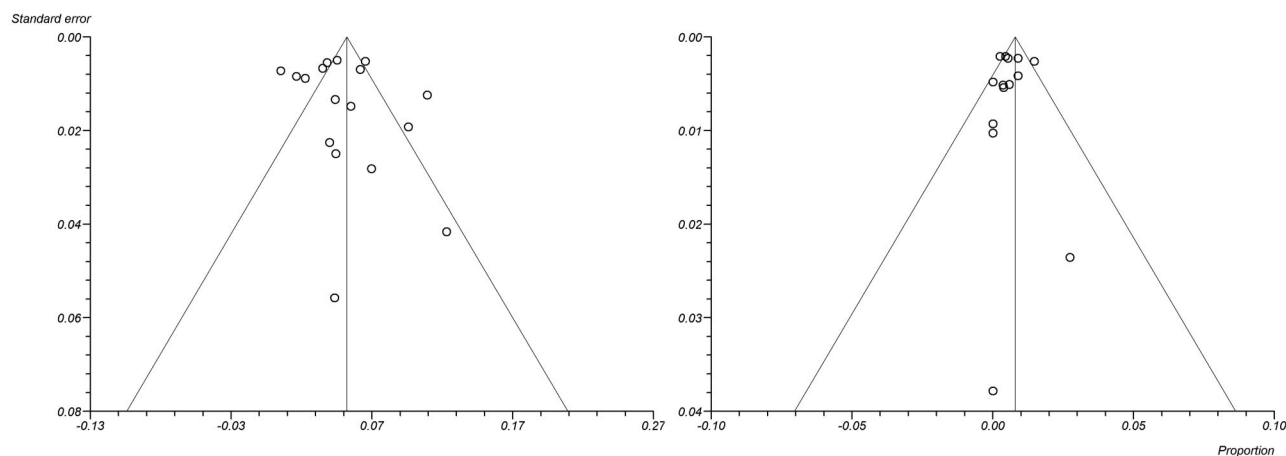


Fig. 5. Funnel plots comparing the proportions versus the standard error of the proportions for intracranial hemorrhage (left) and serious bleeding event (right) at 28 days in patients who had received activated protein C. There was no evidence of publication bias.

be scattered above and below the summary estimate, producing a triangular or funnel shape.¹⁸⁻²⁰

We also checked for publication bias with the Egger test,¹⁸ which tests the asymmetry of the funnel plot. This is a test for the Y intercept = 0 from a linear regression of normalized effect estimate (estimate divided by its standard error) against precision (reciprocal of the standard error of the estimate).

Sensitivity Analysis

We performed sensitivity analyses to examine the bleeding rates when only specific study types were included (ie, observational or RCT), and the difference between the study designs were analyzed with the chi-square test.

Institutional review board clearance was not required for this study, as this was a meta-analysis of published studies.

Results

Our initial database search retrieved 965 citations, of which 948 were excluded because they did not meet our inclusion criteria (Fig. 1). Finally, 17 studies met our inclusion criteria and were included in the final analysis.^{3,4,21-35} The studies were from around the globe and involved administration of activated protein C for management of severe sepsis. Twelve studies were observational^{22-27,29-33,35} and five were RCTs.^{3,4,21,28,34} Eight were prospective^{3,4,21-23,28,33,34} and nine were retrospective^{24-27,29-32,35} (Table 1). The studies' inclusion and exclusion criteria and definitions of serious bleeding event are given in Table 2.

Table 3. Sensitivity Analysis on the Rate of Bleeding Events in Patients Who Received Activated Protein C

	Randomized Controlled Trials (<i>n</i> = 5)					Observational Studies (<i>n</i> = 12)						
	Events (<i>n</i>)	Total Patients (<i>N</i>)	Event Rate* (%)	95% CI	References	Events (<i>n</i>)	Total Patients (<i>N</i>)	Event Rate (%)	95% CI	References	<i>P</i> †	
During Infusion												
Serious bleeding events	109	4,584	2.4	1.8–3.1	3, 4, 21, 28, 34	122	2,986	5	3–8	23, 27, 32, 35	< .001	
Intracranial hemorrhage	13	4,584	0.33	0.18–0.51	3, 4, 21, 28, 34	18	2,986	0.65	0.4–0.98	23, 27, 32, 35	.03	
At 28 Days												
Serious bleeding events	174	4,584	3.6	2.5–4.8	3, 4, 21, 28, 34	394	6,095	6	4.5–7.8	22–27, 29–33, 35	< .001	
Intracranial hemorrhage	25	4,584	0.52	0.26–0.85	3, 4, 21, 28, 34	55	5,693	0.87	0.55–1.3	22–23, 25–27, 29–32, 35	.02	
* Event rate = events/total patients.												
† Via chi-square test.												

* Event rate = events/total patients.

† Via chi-square test.

Bleeding Rates During Infusion of Activated Protein C

Nine studies (7,570 subjects, 4,584 in 5 RCTs^{3,4,21,28,34} and 2,986 in 4 observational studies^{23,27,32,35}) reported serious bleeding events and intracranial hemorrhage during activated protein C infusion. The occurrence of serious bleeding events ranged from 0.5% to 9.6%, and the pooled prevalence was 3.3% (95% CI 2.4–4.4%) by the random effects model (Fig. 2). The occurrence of intracranial hemorrhage ranged from 0% to 1.4%, and the pooled prevalence was 0.44% (95% CI 0.31–0.6%) (see Fig. 2). There was significant statistical heterogeneity for the outcome of serious bleeding event (I^2 76.6, 95% CI 48.7–86.3, Cochran Q statistic 34.26, $P < .001$). There was no statistical heterogeneity for the outcome of intracranial hemorrhage (I^2 zero, 95% CI 0–54.4, Cochran Q statistic 5.95, $P < .001$).

The funnel plots showed minimal evidence of publication bias (Fig. 3). However, the statistical test showed no evidence of publication bias for either outcome (serious bleeding event Egger bias 1.53, $P = .24$; intracranial hemorrhage Egger bias 0.01, $P = .99$), which suggests no meaningful bias.

Bleeding Rates at 28 Days

Seventeen studies (10,679 subjects) reported serious bleeding events at 28 days, and 15 studies (10,277 subjects, 4,584 in 5 RCTs^{3,4,21,28,34} and 5,693 in 10 observational studies^{22,23,25–27,29–32,35}) reported intracranial hemorrhage at 28 days. The occurrence of serious bleeding events ranged from 0.5% to 12.3%, and the pooled prevalence was 5.1% (95% CI 3.9–6.4%) (Fig. 4). The occurrence of intracranial hemorrhage ranged from 0% to 2.7%, and the pooled prevalence was 0.7% (95% CI 0.47–0.98%) (see Fig. 4).

There was significant statistical heterogeneity for the both the outcomes (serious bleeding event I^2 84.5, 95% CI 76.4–88.9, Cochran Q statistic 103.27, $P < .001$; intracranial hemorrhage I^2 44, 95% CI 0–68.1, Cochran Q statistic 24.99, $P = .03$). The funnel plots showed minimal evidence of publication bias (Fig. 5). However, the statistical test showed no evidence of publication bias for either outcome (serious bleeding event Egger bias 0.89, $P = .85$; intracranial hemorrhage Egger bias -0.2 , $P = .75$), which again suggests no meaningful bias.

Sensitivity Analysis

Sensitivity analysis for study type (ie, RCT or observational) revealed that both serious bleeding events and intracranial hemorrhage during infusion and at 28 days were significantly higher in the observational studies than in the RCTs (Table 3).

Discussion

The results of this study suggest that the cumulative prevalence of serious bleeding events with activated protein C is around 3.3% during infusion and 5.1% at 28 days. The rates of intracranial hemorrhage are around 0.4% and 0.7%, respectively, during infusion and at 28 days. The majority of bleeding events were reported during infusion, which is expected because the activated protein C anticoagulant action lasts approximately 2 hours.³⁶ Thus, activated protein C should be judiciously used in any patient with severe sepsis who is a candidate for its use.

The bleeding rates were higher in the observational studies than in the RCTs. One obvious reason is the retrospective nature of observational studies, which generally limits the quality and completeness of data. Furthermore, the definitions of a serious bleeding event were not similar across the observational studies. In some of the observational studies a sizeable proportion of patients had baseline bleeding risk or relative contraindications to activated protein C,^{26,27,32,35} which would have necessitated exclusion from the PROWESS trial (Table 4). All these factors may be responsible for the higher rate of serious bleeding events in the observational studies, which highlights the importance of proper patient selection for a treatment associated with important complications.

The study by Gentry et al had the highest occurrence of serious bleeding events, because they examined the effects of activated protein C in patients regardless of the bleeding risk.³⁵ In fact, 27 of 73 patients had at least one criterion that would have excluded them from the PROWESS trial, and 20 of them had baseline bleeding risk, for various reasons.³⁵ Of the total 9 serious bleeding events, 7 occurred in patients with baseline bleeding risk.³⁵ Also, the definition of a serious bleeding event was markedly different from that of the original PROWESS study.³

Bertolini et al, in their retrospective review of data, reported that 41.4% of the activated protein C use was off-label (patient age < 18 y, patients without sepsis-associated multi-organ dysfunction, activated protein C administered after 48 h of first organ dysfunction, and thrombocytopenia $< 30,000/\mu\text{L}$).²⁶

In the study by Kanji et al, 44% of the patients had ≥ 4 -organ failure, and 20% of the patients had a relative contraindication to activated protein C, which could have been responsible for the high incidence of bleeding in that study.²⁷ The study by Wheeler et al included 48% of patients (133 of 274) who would have been excluded from the PROWESS trial due to treatment more than 2 days after the severe sepsis documentation (93 patients, 70%) and presence of severe coagulopathy (40 patients, 30%) and body weight > 135 kg.³²

On the other hand, in the RCTs designed to evaluate efficacy, the exclusion criteria were rigorously maintained to

Table 4. PROWESS Trial³ Inclusion and Exclusion Criteria and Definition of Serious Bleeding Event

Inclusion Criteria
Evidence of infection
Modified systemic inflammatory response syndrome (SIRS) criteria: at least 3 of 4 criteria of temperature, heart rate, respiratory rate, and white-blood-cell count.
Sepsis-induced organ dysfunction criteria: at least one of the following organ dysfunctions: cardiovascular, renal, hematological, metabolic
Exclusion Criteria
Pregnant or lactating
< 18 y old
Weight > 135 kg
High risk of bleeding
Surgery within 12 h or potential need for such surgery during the infusion
Evidence of active postoperative bleeding
History of severe head trauma requiring hospitalization, intracranial surgery, or stroke within 3 months
History of intracerebral arteriovenous malformation, cerebral aneurysm, or mass lesions of the central nervous system
History of congenital bleeding diathesis
Gastrointestinal bleeding in the past 6 weeks, unless corrective surgery had been performed
Trauma considered to increase the risk of bleeding
Known hypercoagulable condition
Family, physician, or both not in favor of aggressive treatment
Not expected to survive 28 d because of uncorrectable medical condition or moribund state in which death is perceived to be imminent
Organ transplantation
Chronic renal failure requiring hemodialysis or peritoneal dialysis
Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis, or chronic ascites, acute pancreatitis with no established source of infection
Use of medications or treatment regimens such as low-molecular- weight or unfractionated heparin in therapeutic doses within past 12 h before infusion, or warfarin within past 7 d, acetylsalicylic acid at > 650 mg/d within 3 d before the study
Thrombolytic therapy within 3 d before the study
Glycoprotein IIb/IIIa antagonists within 7 d
Protein C within 24 h
Antithrombin III at a dose of >10,000 U within 12 h before the study
Definition of Serious Bleeding Event
Any intracranial hemorrhage
Any life-threatening bleeding
Any bleeding event classified as serious by the investigator
Any bleeding that required administration of 3 units of packed red blood cells on 2 consecutive days

lessen the adverse events. Approximately 68% of patients in our meta-analysis received the study drug under controlled conditions, and the bleeding rates were similar to that of the PROWESS trial in that subgroup. Bernard et al, in a safety assessment study of activated protein C, included all trials till 2002 (2,786 patients), and found a cumulative serious-bleeding-event rate of 2.8% ($n = 79$, 95% CI 2.3–3.5%) during infusion and 5.3% ($n = 148$, 95% CI 4.0–6.4%) at 28 days.⁵

Thrombocytopenia and invasive procedures were identified as significant risk factors for serious bleeding events. A

platelet count < 50,000/ μ L accounted for 41.5% of the serious bleeding events during infusion across all the trials studied. In the PROWESS trial,³ 53.3% of serious bleeding events in the treatment arm and 23.5% in the placebo arm were related to invasive procedures, whereas it was 39.2% across all the trials in the study by Bernard et al.⁵ However, in clinical practice such strict inclusion and exclusion criteria are not strictly adhered to, leading to a higher chance of adverse events. Hence, in day-to-day practice the bleeding rate is likely to be somewhere between the rates reported in the RCTs and the observational studies, as reported in this study.

Bleeding complications are an inherent risk of all drugs with anticoagulant activity, including heparins, warfarin, and anti-platelet agents. However, excessive bleeding in trial conditions has not prevented various anticoagulants from being used in the treatment of acute myocardial infarction and pulmonary embolism. Similarly, patients with severe sepsis should not be denied a therapy with proven efficacy just because of bleeding risk. However, the bleeding rates we found in this meta-analysis would certainly outweigh the survival benefit in daily practice. Hence, strict adherence to inclusion and exclusion criteria to screen patients before infusion, and judiciously managing infusion during invasive procedures will certainly reduce the bleeding. This study also emphasizes the need for formulation of strict practice guidelines for the use of activated protein C in countries where it has been approved.

Limitations

As this was an abstract patient-data meta-analysis, we did not know the baseline characteristics of the patients who had serious bleeding events and intracranial hemorrhage, such as platelet count, coagulation profile, and performance of invasive procedures. Because the company that manufactures the drug (Eli Lilly) maintains a registry of the indications, baseline characteristics, and outcomes of all the patients who have received the drug, an individual patient-data meta-analysis should be performed, which would strengthen the results of this study and replicate actual clinical practice.

The other limitation of this meta-analysis is the presence of statistical and clinical heterogeneity, although we did try to compensate for the statistical heterogeneity by using a random-effects model. Ideally a meta-analysis should be considered only when the individual studies are sufficiently homogeneous in terms of participants, interventions, and outcomes, so that one can reasonably expect the same magnitude of effect across the range of patients, interventions, and outcomes of the various studies. However, one can also argue that since clinical diversity always occurs in any 2 studies included in a meta-analysis, statistical heterogeneity is inevitable.

Conclusions

Activated protein C is associated with significant risk of bleeding, and the bleeding risk was higher in the observational studies than in the RCTs. Clinicians should consider these rates of serious bleeding events and intracranial hemorrhage before administering activated protein C, and explicitly weigh the risk-benefit ratio of this therapy.

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